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Patent

Attorney's Docket No. 003300-763

6/14/01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

JOHN KENDRUP et al.

Application No.: 09/819,813

Filed: March 29, 2001

For: METHOD FOR PRODUCING A CONTROLLED-RELEASE COMPOSITION

Group Art Unit: 1615

Examiner: Unassigned

CLAIM FOR CONVENTION PRIORITY

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The benefit of the filing date of the following prior foreign Patent Application in the following foreign country is hereby requested, and the right of priority provided in 35 U.S.C. § 119 is hereby claimed:

Swedish Patent Application No. 0001151-0

Filed: March 31, 2000

In support of this claim, enclosed is a certified copy of said prior foreign Patent Application. Said prior foreign Patent Application is referred to in the oath or declaration. Acknowledgment of receipt of the certified copy is requested.

Respectfully submitted,

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Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

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(21) *Patentansökningsnummer* *0001151-0*
Patent application number

(86) *Ingivningsdatum* *2000-03-31*
Date of filing

Stockholm, 2001-04-04

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For the Patent- and Registration Office

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METHOD FOR PRODUCING A CONTROLLED-RELEASE COMPOSITION

FIELD OF THE INVENTION

The present invention concerns a method for producing a pharmaceutical composition. Specifically the invention concerns a method for producing a controlled-release pharmaceutical composition with a pore-containing coating, the coating being derived from an aqueous dispersion of a film-forming water insoluble polymer and a pore-forming agent.

BACKGROUND OF THE INVENTION

Many types of controlled release tablets are known, which have had greater or lesser degrees of success accomplishing the desired result, namely the attainment of a substantially constant and controlled dissolution rate during a major portion of their dissolution time when exposed to gastrointestinal fluids. One such tablet is disclosed in US 4,557,925. Medical preparations developed according to this patent are currently used and well accepted by the patients. The tablet comprises a drug-containing tablet core and a water-insoluble coating surrounding the same, wherein the coating contains a pore-creating agent. The tablet is produced with a method according to which the water insoluble coating-polymer is first dissolved in an organic solvent, i.e. aceton, before the coating process.

Lately environmental and safety concern have restricted medical companies in the use of organic solvents in their processes. The answer to this restriction is pharmaceutical compositions coated with aqueous dispersions of water insoluble film-forming polymers. Such compositions are described in US 5,472,712, the coatings therein having a water-soluble release-modifying agent. The release-modifying agent is functioning as a pore-

former and is dissolved in the aqueous dispersion of the film-polymer before the coating process. A problem with compositions having such coatings is the slow release of drugs through the coatings. Another problem is the poor strength of the coating.

OBJECT OF THE INVENTION

An object of the present invention is therefore to accomplish a method for producing a controlled-release pharamaceutical composition, the composition having the same effective release rate as the one described in US 4,557,925 while avoiding the use of organic solvents and the problems arising by using the method according to US 5,472,712.

SUMMARY OF THE INVENTION

This object as well as other objects that will be apparent from the description below, have now been obtained according to the present invention by providing a method for producing an essentially zero order controlled-release pharmaceutical composition with a pore-containing coating according to claim 1, having excellent strength and reproducibility.

Thus the method according to the invention entails suspending a pore-forming agent in an aqueous dispersion of a water insoluble film-forming polymer and thereafter coating a solid drug-containing core with the suspension of pore-former and polymer. By suspending, instead of dissolving, the pore-forming agent, the resulting coating will contain larger sized pore-formers that creates, when dissolved in the body fluid, canals or a network through the membrane in the polymer. Due to this network, the membranes have a good mechanical stability, gives fast release of the drug and are left intact after the release of the drug.

DETAILED DESCRIPTION OF THE INVENTION

The pore-forming agent according to the present invention can be any substance that can be dispersed in an aqueous dispersion of the coating-polymer, without being completely dissolved and that form pores or canals in the complete coating when dissolved by body fluids.

An important factor for the pore-forming agent is thus its solubility and mean particle size. The mean particle size is 0,5-500 µm, preferably 1,0-100 µm and most preferably 1,0-20 µm.

The solubility of the pore-forming agent is preferably below 200 mg/ml in pure water at 25°C. The solubility of the pore-forming agent in the aqueous coating dispersion is below 100 mg/ml, preferably below 50 and most preferably below 30 mg/ml.

The pore-forming agent could be selected from a group consisting of potassium salts, calcium salts, magnesium salts, amino acids, week acids, carbohydrates, polymers with amino and/or acid functions. The pore-former can also be a composition wherein at least one of the components is selected from one of these groups.

In a preferred embodiment the pore-forming agent is potassium hydrogen tartrate.

Other preferred pore-forming agents are chitosan and poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1:2:1.

The film-forming polymer according to the present invention could be any pharmaceutically acceptable water insoluble polymer, block- or copolymer that can be dispersed in an aqueous solution. Example of such polymers are polymers selected from the groups consisting of cellulose esters, acrylic polymers, polyvinyl acetates, polyvinyl chlorides or a composition wherein at least one component is selected from one of the groups.

Preferred substances are polyvinylacetate, polymethylmetacrylate or a terpolymer of vinylchloride, vinylalcohol and vinylacetate. Commercialy available latexes,

pseudolatexes and polymer emulsions are also possible to use for the coating.

In a preferred embodiment of the invention the coating-agent is a water-dispersion of the terpolymer from US 4,557,925, consisting of 80-95% by weight of polyvinylchloride, 0,5-19% by weight of polyvinylacetate and 0,5-10% by weight of polyvinylalcohol.

In another preferred embodiment of the invention the coating agent is a copolymer consisting of 50-100% by weight of polyvinylchloride and 0-50% by weight of polyvinylacetate.

The weight ratio, amount of pore-forming agent to total weight of the dry coating, depends on the chosen polymer and pore-former and the release pattern desired, but is normally between 50 and 90% by weight.

A plasticiser may be added to adjust the softening temperature (Tg) of the polymer. The Tg is an important factor for regulating the mechanical properties of the polymer.

The pore-forming agent in the coating suspension is preferably stabilized with one or more ionic, non-ionic or polymer surfactants.

The aqueous dispersion of the polymer and the pore-forming agent may be used to coat solid cores such as crystals, granules, pellets, tablets or the like.

The aqueous dispersion of the polymer and the pore-forming agent is preferably spray-coated onto the solid cores.

The obtained coated cores may be cured with heat or moisture.

The drug in the solid core could for example be tranquillizers, antibiotics, hypnotics, antihypertensives, antianginics, analgesics, antiinflamatories, neuroleptics, antidiabetics, diuretics, antikolinergics, antihyperacidics, antiepileptics, ACE inhibitors, β-receptor antagonists and agonists, anaesthetics, anorexiants, antiarrythmics, antidepressants,

anticoagulants, antidiarrhoetics, antihistamines, antimalariels, antineoplastics, immunosuppressives, antiparkinsonians, antipsychotics, antiplatelets, diuretics or antihyperlipidics.

The drug substance could for example be potassium chloride, theophylline, a theophylline salt, phenyl-propanolamine, sodium salicylate, paracetamole, carbidopa, levodopa, diltiazem, enalapril, verapamil, naproxen, pseudoephedrin, nicorandil, oxybutuin, morphine, oxycodone or propranolol.

The aqueous suspension of pore-former and polymer can be diluted with an organic solvent up to 20%, preferably up to 10% and most preferably up to 5%. The organic solvent plasticise the polymer to enhance film formation. The organic solvent also decreases the solubility of the pore-former in the suspension.

The present invention is not limited in its method aspect by the drug or type of drug incorporated in the composition. Any composition containing any presently known or future discovered orally acting drug may be coated according to the present invention, to provide the highly advantageous controlled release pharmaceutical compositions of the present invention.

The invention is further illustrated by, but should not be limited to, the following preparations and example.

Example

Core

The composition of the core is shown in table 1. The ingredients are granulated in a high shear mixer, dried and milled thereafter. The material is blended with lubricants and then compressed to tablets in a tablet press.

TABLE 1

Ingredients	(mg/tablet)
Diltiazem hydrochloride	350
Sodium dihydrogen citrate	218
Povidone K25	42,4
Magnesium stearate	12,5
Ethanol*	45,4
Total	623

*Evaporates during the process

Coating suspension

The composition of a coating is shown in table 2. The coating suspension was prepared by adding the polymer dispersion, the pore former (with a specific particle size) and deionised water to a final content of dry substances of 15% w/w, to a continously stirred container.

TABLE 2

Ingredients	(%/membrane)	Dry weight (mg)
Polymer dispersion-Polyvinylacetate (water dispersion)	30	21
Potassium bitartrate (D50≈27µm)	70	49
Deionised water*		397*
Total (mg)		70
Total (mg/cm^2)		20

*Evaporates during the process

Coating

The cores were coated with the coating suspension in a coating pan. The coated tablets were allowed to dry in the pan for 15 minutes.

Different embodiments of the composition according to the invention, shown in table 3, are made accordingly.

TABLE 3

Batch	Core (Diltiazem)	Coating				
		Film weight	Pore-former		Coating agent	
	(mg)	(mg/cm^2)	Type	(%)	Type	(%)
1	350	20	KHT[1]	0	PVAc[2]	100
2	350	4,8	KHT[1]	0	PVAc[2]	100
3	350	20	KHT[1]	80	PVAc[2]	20
4	350	20	KHT[1]	60	PVAc[2]	40
5	320[3]	24	KHT[1]	70	P(EA-MMA)[4]	30

[1] KHT=Potassium bitartrate

[2] PVAc=Polyvinylacetate

[3] 100 mg of Polyethyleneoxid is included in the formulation

[4] P(EA-MMA)=Poly(ethylacrylate-methylmethacrylate) 2:1

Results

Table 4 shows results from an in vitro dissolution test (according to USP 23, paddle method) with the formulations from table 3.

Batch number 1 and 2 with no added pore-former have a very slow release pattern. The addition of pore-former (batch 3-5) increases the release rate and makes it

possible to design formulations according to a desired release pattern.

Batch 2 and 4 had comparable drug-release rates. However, the films from batch 2 ruptured during the analysis. Batch 4 showed much less variability in drug release compared to batch 2 and the film still had good mechanical strength after the analysis.

TABLE 4

Batch	Amount released Diltiazem (%) after x hours (pH 6,8)								Range at 40% released Diltiazem	
	1h	2h	4h	8h	12h	24h	48h	96h	(%)	n
1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,6	-	6
2	1,6	3,7	7,0	14,9	22,2	41,7	89,4	101,3	17,7	3
3	10,1	26,8	50,8	81,6	93,2	97,0	-	-	2,2	6
4	0,4	0,6	1,5	8,5	19,7	41,2	-	-	3,5	6
5	3,0	15,0	35,1	65,1	89,3	101,4	-	-	7,2	6

CLAIMS

1. A method for producing a controlled-release pharmaceutical composition with a pore-containing coating comprising the steps of:

a) preparing a drug-containing solid core;

b) suspending a pore-forming agent, having a mean particle size of 0,5-500 µm, in an aqueous dispersion of a film-forming water insoluble agent;

c) coating the solid core with the aqueous suspension of the pore-forming agent and the film-forming agent in order to obtain a coating on the core;

the pore-forming agent forming pores or canals when dissolving from the obtained coating.

2. A method according to claim 1, wherein the solubility of the pore-forming agent is below 100 mg/ml, preferably below 50 and most preferably below 30 mg/ml in the aqueous coating dispersion.

3. A method according to claim 1 or 2, wherein the solubility of the pore-forming agent is higher in the body-fluids than in the aqueous coating dispersion.

4. A method according to any of the claims 1-3, wherein the mean particle size of the pore-forming agent preferably is 1-100 µm and most preferably 1-20 µm.

5. A method according to any of the claims 1-4, wherein the amount of the pore-forming agent to the total weight of the dry coating is 50-90% by weight.

6. A method according to any of the claims 1-5, wherein the coating agent is any water insoluble polymer or a composition wherein at least one component is a water insoluble polymer.

7. A method according to any of the claims 1-6, wherein the coating agent is any water insoluble polymer, block- or copolymer, selected from one of the groups of cellulose esters, acrylic polymers, polyvinyl acetates, polyvinyl chlorides or a composition wherein at least one component is selected from one of the groups.

8. A method according to any of the claims 1-7, wherein the coating agent is ethylcellulose, cellulose-acetate, celluloseacetatebutyrate, celluloseacetate-propionate, nitrocellulose, polymethylmethacrylate, poly(ethylacrylate, methylmetacrylate), polyvinylacetate, polyvinylchloride, polyethylene, polyisobutylene, poly(ethylacrylate, methylmetacrylate, trimethylamonioethylmetacrylatchloride), a block- or copolymer of the polymers or a composition wherein at least one of the components is selected from these polymers.

9. A method according to any of the claims 1-8, wherein the coating agent is a copolymer consisting of 50-100% by weight of polyvinylchloride and 0-50% by weight of polyvinylacetate.

10. A method according to any of the claims 1-9, wherein the coating agent is a copolymer consisting of 80-95% by weight of polyvinylchloride, 0,5-19% by weight of polyvinylacetate and 0,5-10% by weight of polyvinyl-alcohol.

11. A method according to any of the claims 1-10, wherein the pore-forming agent is selected from a group consisting of potassium salts, calcium salts, magnesium salts, amino acids, week acids, carbohydrates, polymers with amino and/or acid functions or a composition wherein at least one of the components is selected from one of these groups.

12. A method according to any of the claims 1-11, wherein the pore-forming agent is potassiumbitartrate, creatine, aspargine, glutamine, aspartic acid, glutamic acid, leucin, neroleucine, inosine, isoleucine, magnesium citrate, magnesium phosphate, magnesium carbonate, magnesium hydroxide, magnesium oxide or a composition wherein at least one component is selected from one of these substances.

13. A method according to any of the claims 1-12, wherein the pore-forming agent is chitosan and poly(butyl

methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1:2:1.

14. A method according to any of the claims 1-13, wherein the drug for the solid core is selected from the group consisting of tranquillizers, antibiotics, hypnotics, antihypertensives, antianginas, analgesics, antiinflamatorics, neuroleptics, antidiabetics, diuretics, anticholinergics, antihyperacidics or antiepileptics, ACE inhibitors, β-receptor antagonists and agonists, anaesthetics, anorexiants, antiarrythmics, antidepressants, anticoagulants, antidiarrhoetics, antihistamines, antimalariels, antineoplastics, immunosuppressives, antiparkinsonians, antipsychotics, antiplatelets, diuretics, antihyperlipidics.

15. A method according to any of the claims 1-14, wherein the drug for the solid core is potassium chloride, theophylline, a theophylline salt, phenylpropanolamine, sodium salicylate, choline theophyllinate, paracetamole, carbidopa, levodopa, diltiazem, enalapril, verapamil, naproxen, pseudoephedrin, nicorandil, oxybutuin, morphine, oxycodone or propranolol.

16. A method according to any of the claims 1-15, wherein the aqueous dispersion is diluted with an organic solvent to up to 20%, preferably up to 10% and most preferably up to 5%.

17. A method according to any of the claims 1-16, wherein the obtained coated cores are cured with heat or moisture.

18. A method according to any of the claims 1-17, wherein the pore-former in the coating suspension is stabilized with one or more ionic, non-ionic or polymer surfactants.

19. A method according to any of the claims 1-18, wherein the coating agent is plasticized.

ABSTRACT

A method for producing a controlled-release pharmaceutical composition with a pore-containing coating, the coating being derived from an aqueous dispersion of a film-forming water insoluble polymer and a pore-forming agent. By suspending, instead of dissolving the pore-forming agent, the resulting coating will contain larger sized pore-formers that creates, when dissintegrated in the body fluid, canals or a network through the membrane in the polymer. Due to this network, the membranes have a good mechanical stability and are left intact after the release of the drug.